

to target nucleic acid sequence, wherein said virtual compounds modulate the expression of a target nucleic acid sequence;

synthesizing compounds corresponding to at least some of said virtual compounds; and
robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

56. (Twice Amended) A method comprising:

evaluating *in silico* a plurality of virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

58. (Twice Amended) A method comprising:

generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

59. (Twice Amended) A method comprising:

c² evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties.

c³ 72. (Twice Amended) A method comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

c⁴ 74. (Twice Amended) A method comprising:

generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides having said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

75. (Twice Amended) A method comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

78. (Twice Amended) A method comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

79. (Twice Amended) A method comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

80. (Twice Amended) A method comprising:

- a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;
- b) choosing an oligonucleotide chemistry;
- c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;
- d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);
- e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and
- f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

81. (Twice Amended) A method comprising:

- evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and
- robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

82. (Twice Amended) A method comprising:

- a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

85. (Twice Amended) A method comprising:

ck a) evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

86. (Twice Amended) A method comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

87. (Twice Amended) A method comprising: